

What is claimed is:

- Sub a1* 1. A method to regulate body weight in an animal, comprising administering to said animal a therapeutic composition comprising a proopiomelanocortin (POMC) compound, wherein said POMC compound is administered to the periphery of said animal in an amount effective to measurably regulate body weight in said animal, whereby administration of said compound minimizes delivery of said compound to the central nervous system of said animal.
2. The method of Claim 1, wherein said compound is selected from the group consisting of a melanocortin compound and a lipocortin compound.
3. The method of Claim 1, wherein said compound is a melanocortin compound.
- Sub a2* 4. The method of Claim 1, wherein said compound is selected from the group consisting of melanocyte stimulating hormone (MSH), a fragment of MSH, a homologue of MSH, a peptide mimetic of MSH, a non-peptide mimetic of MSH, and a fusion protein comprising an MSH protein or fragment thereof.
- Sub a2* 5. The method of Claim 1, wherein said compound is selected from the group consisting of  $\alpha$ -MSH,  $\beta$ -MSH and  $\gamma$ -MSH.
- Sub a3* 6. The method of Claim 1, wherein said compound is a peptide mimetic of MSH.
7. The method of Claim 1, wherein said compound is an analog of a peptide having an amino acid sequence represented herein by SEQ ID NO:2.
- Sub a4* 8. The method of Claim 1, wherein said POMC compound is an  $\alpha$ -MSH analog selected from the group consisting of:
- [Ac-Cys<sup>4</sup>, D-Phe<sup>7</sup>, Cys<sup>10</sup>]  $\alpha$ -MSH, wherein said Cys residues are connected by a disulfide bond;
  - Ac-[Nle<sup>4</sup>, X<sub>aa</sub><sup>5</sup>, His<sup>6</sup>, X<sub>aa</sub><sup>7</sup>, Arg<sup>7</sup>, Trp<sup>9</sup>, X<sub>aa</sub><sup>10</sup>]-NH<sub>2</sub>, (SEQ ID NO:3) wherein X<sub>aa</sub><sup>5</sup> is Glu or Asp, X<sub>aa</sub><sup>7</sup> is Phe or D-Phe and X<sub>aa</sub><sup>10</sup> is a dibasic amino acid; Lys; ornithine; 2,4,-diaminobutyric acid; or 2,3 diaminopropionic acid (Dpr);

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(8. prev. beginning 12/9/99)

c.  $\text{Ac}[\text{Cys}^4, \text{Cys}^{10}]\alpha\text{-MSH}_{1-13}\text{NH}_2$ ;

d.  $\text{R}_1\text{-W-X-Y-Z-R}_2$ ,

wherein  $\text{R}_1$  is selected from the group consisting of Ac-Gly-, Ac-Met-Glu-, Ac-Nle-Glu- and Ac-Tyr-Glu-;

W is selected from the group consisting of -His- and -D-His-;

X is selected from the group consisting of -Phe-, -D-Phe-, -Tyr-, -D-Tyr-, (-pNO<sub>2</sub>)D-Phe<sup>7</sup>-;

Y is selected from the group consisting of -Arg- and -D-Arg-;

Z is selected from the group consisting of -Trp- and -D-Trp-; and,

$\text{R}_2$  is selected from the group consisting of -NH<sub>2</sub>, -Gly-NH<sub>2</sub>, and -Gly-Lys-NH<sub>2</sub>;

e.  $\text{Ac-Ser-Tyr-Ser-M-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH}_2$  (SEQ ID NO:4),

wherein M is selected from the group consisting of Met, Nle, and Cys;

f.  $[\text{Nle}^4, \text{D-Phe}^7]\text{-}\alpha\text{-MSH}$ ;

g.  $[\text{Nle}^4, \text{D-Phe}^7]\text{-}\alpha\text{-MSH}_{4-10}$ ;

h.  $[\text{Nle}^4, \text{D-Phe}^7]\text{-}\alpha\text{-MSH}_{4-11}$ ;

i.  $[\text{Nle}^4, \text{D-Phe}^7, \text{D-Trp}^9]\text{-}\alpha\text{-MSH}_{4-11}$ ;

j.  $[\text{Nle}^4, \text{D-Phe}^7]\text{-}\alpha\text{-MSH}_{4-9}$ ;

k.  $\text{Ac}[\text{Nle}^4, \text{AA}^5, \text{D-Phe}^7, \text{AA}^{10}]\text{-R}_1$  or  $\text{Ac}[\text{Nle}^4, \text{AA}^5, \text{D-Phe}^7, \text{AA}^{11}]\text{-R}_2$ ;

wherein AA<sup>5</sup> may be either a L- or D- amino acid having an omega amino or carboxyl group in the side chain, e.g.,  $\alpha,\gamma$ -diaminopropionic acid,  $\alpha,\gamma$ -diaminobutyric acid, Orn, Lys,  $\alpha,\beta$ -aminoadipic acid,  $\alpha$ -aminopimelic acid, or higher homologs, Glu or Asp;

wherein AA<sup>10</sup> may be diaminopropionic acid,  $\alpha,\gamma$ -diaminobutyric acid, Orn, Lys,  $\alpha,\beta$ -aminoadipic acid,  $\alpha$ -aminopimelic acid, or higher homologs, Glu or Asp;

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wherein R<sub>1</sub> is the designation  $\alpha$ -MSH<sub>1-13</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>1-12</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>1-11</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>4-13</sub>NH<sub>2</sub>, or  $\alpha$ -MSH<sub>4-10</sub>NH<sub>2</sub>;

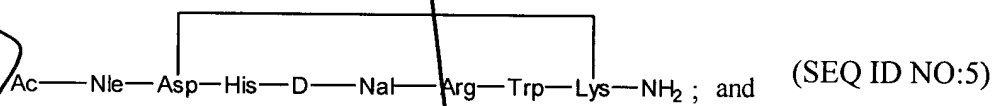
wherein AA<sup>11</sup> may be L- or D- amino acid having an omega-amino or carboxyl group in the side chain, e.g.,  $\alpha,\beta$ -diaminopropionic acid;  $\alpha,\gamma$ -diaminobutyric acid, Orn, Lys,  $\alpha$ -aminoadipic acid,  $\alpha$ -aminopimelic acid, or higher homologs, Glu or Asp;

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wherein R<sub>2</sub> is the designation  $\alpha$ -MSH<sub>1-13</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>1-12</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>1-11</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>4-13</sub>NH<sub>2</sub>, or  $\alpha$ -MSH<sub>4-10</sub>NH<sub>2</sub>; and,

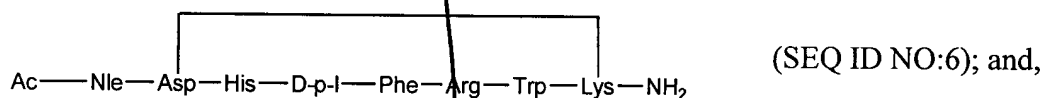
wherein Xxx may be from 1 to 5 a-amino acid residues each of which may be of L- or D- configuration, or a linear or branched chain spacer;

l.



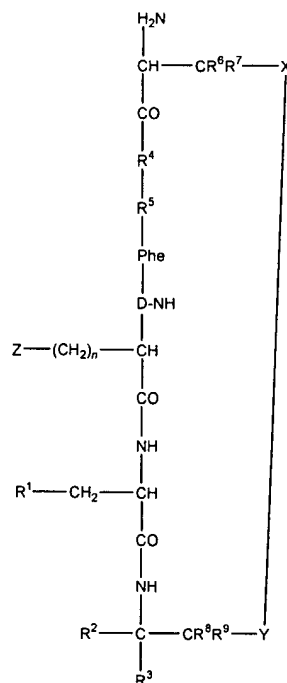
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m.



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n.



wherein  $\text{R}^1$  is a substituted or unsubstituted aromatic radical;

$\text{R}^2$  is hydrogen or a methyl group;

$\text{R}^3$  is a carboxylate, carboxamide, hydroxymethyl, or aldehyde group;

$\text{R}^4$  is glutamic acid, alanine,  $\gamma$ -amino butyric acid, valine, leucine or isoleucine;

$\text{R}^5$  is histidine, glutamic acid, alanine, valine, leucine or isoleucine;

$\text{R}^6$  and  $\text{R}^7$ , which may be the same or different, are hydrogen, methyl or lower alkyl

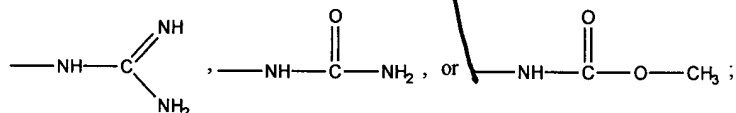
having one to five carbon atoms;

$\text{R}^8$  and  $\text{R}^9$ , which may be the same or different, are hydrogen, methyl or lower alkyl

having one to five carbon atoms;

X and Y are sulfur, methylene, SO or  $\text{SO}_2$ ;

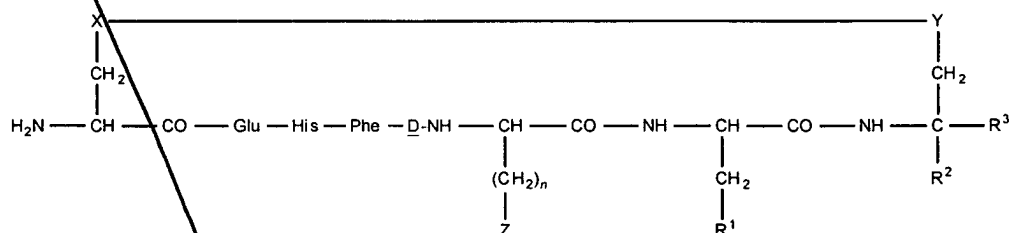
Z is  $-\text{NH}_2$ ,



and,

$n$  is an integer greater than or equal to 2;

O.



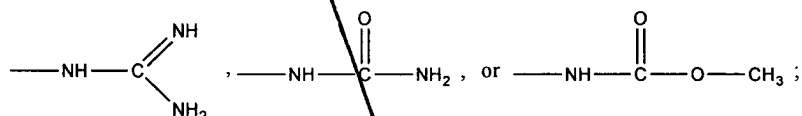
wherein R<sup>1</sup> is phenyl, indole, p-hydroxyphenyl, p-aminophenyl, imidazole, 1-naphthyl, adamantyl or alkylphenyl, 2-naphthyl;

$R^2$  is hydrogen or a methyl group;

R<sup>3</sup> is a carboxylate, carboxamide, hydroxymethyl, or aldehyde group;

X and Y are sulfur, methylene, SO or SO<sub>2</sub>;

Z is  $\text{-NH}_2$ ,



and,

n is an integer greater than or equal to 2; and wherein the cyclized portion of the compound is conformationally restricted in a manner which is compatible with the reactivity of the compound with receptors of the central nervous system.

9. The method of Claim 1, wherein said POMC compound is a peptide comprising an amino acid sequence represented by SEQ ID NO:1.

10. The method of Claim 1, wherein said POMC compound has the following identifying characteristics: (1) an ability to bind to a POMC receptor that is expressed in peripheral tissues; and, (2) a biological activity selected from the group consisting of stimulation of lipolysis and inhibition of the uptake of fatty acids by adipocytes.

11. The method of Claim 10, wherein said POMC receptor is selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R).

12. The method of Claim 10, wherein said POMC receptor is a melanocortin 2-receptor (MC2-R).

*Sub 5* 13. The method of Claim 1, wherein said compound binds to a melanocortin receptor selected from the group consisting of MC2-R and melanocortin 5-receptor (MC5-R), with a higher affinity than to melanocortin-4 receptors (MC4-R).

14. The method of Claim 1, wherein said compound binds to a melanocortin receptor selected from the group consisting of MC2-R and melanocortin 5-receptor (MC5-R), and does not bind to any other melanocortin receptor under physiological conditions.

15. The method of Claim 1, wherein said compound binds to MC2-R, and does not bind to any other melanocortin receptor under physiological conditions.

16. The method of Claim 1, wherein said compound does not bind to MC4-R under physiological conditions.

17. The method of Claim 1, wherein said compound preferentially activates melanocortin-2 receptors (MC2-R) as compared to melanocortin-4 receptors (MC4-R).

18. The method of Claim 1, wherein said compound does not activate MC4-R under physiological conditions.

19. The method of Claim 1, wherein said therapeutic composition is administered transdermally.

20. The method of Claim 1, wherein said therapeutic composition is administered topically.

21. The method of Claim 1, wherein said therapeutic composition is administered parenterally.

22. The method of Claim 1, wherein said therapeutic composition is not administered directly to the central nervous system of said animal.

23. The method of Claim 1, wherein said therapeutic composition is administered in a controlled release formulation.

24. The method of Claim 1, whereby administration of said compound is insufficient to cause a statistically significant change in the appetite of said animal as compared to before administration of said compound.

*Sub 6* 25. The method of Claim 1, wherein said POMC compound is administered in a dose of from about 0.1  $\mu$ g to about 10 mg per kg body weight of said animal.

26. The method of Claim 1, wherein said POMC compound is administered in a dose of from about 1  $\mu$ g to about 10 mg per kg body weight of said animal.

*Sub 7* 27. The method of Claim 1, wherein said POMC compound is administered in a dose of from about 40  $\mu$ g to about 1 mg per kg body weight of said animal.

28. The method of Claim 1, wherein said POMC compound is from about 0.1% to about 90% of said therapeutic composition by weight.

29. The method of Claim 1, wherein said POMC compound is from about 0.1% to about 1% of said therapeutic composition by weight.

*Sub 8* 30. The method of Claim 1, wherein said method is effective to measurably decrease body weight in said animal.

31. The method of Claim 30, wherein said decrease in body weight in said animal can be measured within at least about one week of said step of administering said compound.

*Sub 9* 32. The method of Claim 30, wherein said animal has serum leptin levels between about 0 ng/ml and 50 ng/ml prior to said step of administration.

33. The method of Claim 30, wherein said animal has serum MSH levels between about 0 ng/ml and 10 ng/ml prior to said step of administration.

34. The method of Claim 30, wherein said animal has a ratio of serum MSH levels to serum leptin levels of greater than about 1:100 prior to said step of administration.

35. The method of Claim 30, wherein said animal is a human having a body mass index (BMI) of greater than 27 kilograms per square meter.

36. The method of Claim 30, wherein said composition further comprises another body weight regulating agent.

37. The method of Claim 36, wherein said body weight regulating agent is leptin.

38. The method of Claim 38, wherein said composition comprises a ratio of said POMC compound to leptin of about 1:100.

39. The method of Claim 38, wherein said composition comprises said leptin in a dose of from about 0.1  $\mu$ g to about 100 mg per kg body weight of said animal.

40. The method of Claim 1, wherein said therapeutic composition is administered in an amount effective to measurably increase body weight in said animal or to decrease body weight loss in said animal.

41. The method of Claim 40, wherein said compound is a proopiomelanocortin (POMC) antagonist compound.

42. The method of Claim 41, wherein said compound has the following identifying characteristics: (1) an ability to bind to a POMC receptor that is expressed in peripheral tissues; and, (2) a biological activity selected from the group consisting of inhibition of lipolysis and stimulation of the uptake of fatty acids by adipocytes.

43. The method of Claim 42, wherein said POMC receptor is selected from the group consisting of melanocortin 2-receptor (MC2-R) and melanocortin 5-receptor (MC5-R).

44. The method of Claim 42, wherein said POMC receptor is a melanocortin 2-receptor (MC2-R).

45. The method of Claim 41, wherein said antagonist compound is selected from the group consisting of a melanocortin antagonist compound and a lipocortin antagonist compound.

46. The method of Claim 41, wherein said antagonist compound is a melanocortin antagonist compound.

47. The method of Claim 41, wherein said antagonist compound is selected from the group consisting of a fragment of MSH having MSH antagonist action, a homologue of



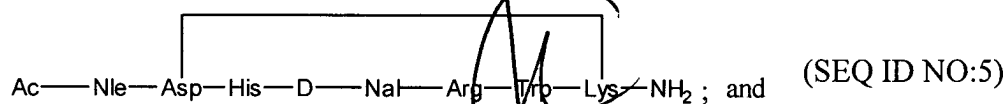
MSH having MSH antagonist action, a peptide mimetic of MSH having MSH antagonist action, a non-peptide mimetic of MSH having MSH antagonist action, and a fusion protein comprising any of said MSH antagonist compounds.

48. The method of Claim 41, wherein said antagonist compound is selected from the group consisting of  $\alpha$ -MSH antagonist,  $\beta$ -MSH antagonist and  $\gamma$ -MSH antagonist.

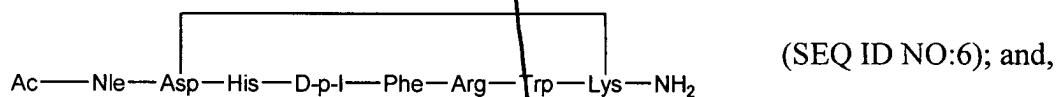
49. The method of Claim 41, wherein said antagonist compound is a peptide mimetic of MSH.

50. The method of Claim 41, wherein said antagonist compound is an MSH analog selected from the group consisting of:

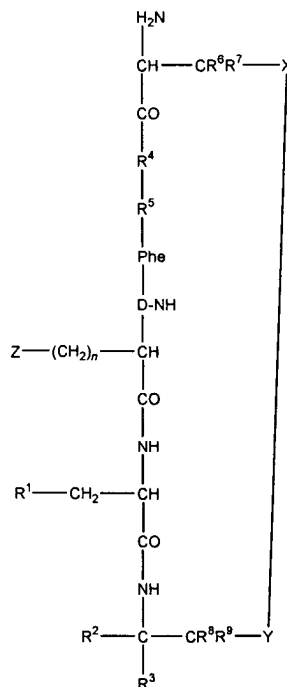
a.



b.



C.



wherein  $\text{R}^1$  is a substituted or unsubstituted aromatic radical;

$\text{R}^2$  is hydrogen or a methyl group;

$\text{R}^3$  is a carboxylate, carboxamide, hydroxymethyl, or aldehyde group;

$\text{R}^4$  is glutamic acid, alanine, -amino butyric acid, valine, leucine or isoleucine;

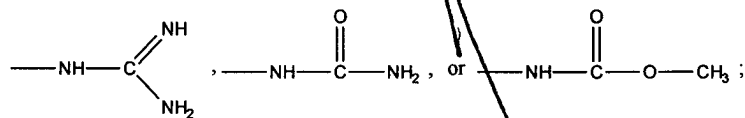
$\text{R}^5$  is histidine, glutamic acid, alanine, valine, leucine or isoleucine;

$\text{R}^6$  and  $\text{R}^7$ , which may be the same or different, are hydrogen, methyl or lower alkyl having one to five carbon atoms;

$\text{R}^8$  and  $\text{R}^9$ , which may be the same or different, are hydrogen, methyl or lower alkyl having one to five carbon atoms;

X and Y are sulfur, methylene, SO or  $\text{SO}_2$ ;

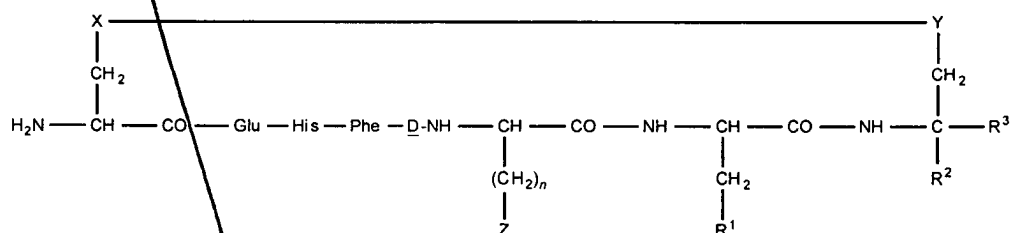
Z is  $-\text{NH}_2$ ,



and,

n is an integer greater than or equal to 2; and,

d.



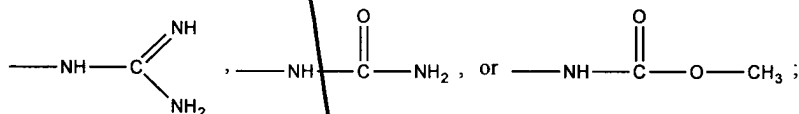
wherein R<sup>1</sup> is phenyl, indole, p-hydroxyphenyl, p-aminophenyl, imidazole, 1-naphthyl, adamantyl or alkylphenyl, 2-naphthyl;

R<sup>2</sup> is hydrogen or a methyl group;

R<sup>3</sup> is a carboxylate, carboxamide, hydroxymethyl, or aldehyde group;

X and Y are sulfur, methylene, SO or SO<sub>2</sub>;

Z is -NH<sub>2</sub>,



and,

n is an integer greater than or equal to 2; and wherein the cyclized portion of the compound is conformationally restricted in a manner which is compatible with the reactivity of the compound with receptors of the central nervous system.

51. The method of Claim 41, wherein said POMC compound is combined with another body weight regulating agent

52. The method of Claim 51, wherein said body weight regulating agent is selected from the group consisting of an anabolic steroid, a growth hormone, erythropoietin, a cytokine, and an anti-cytokine agent.

53. The method of Claim 1, wherein said animal is a human.

54. The method of Claim 1, wherein said composition further comprises an antagonist of MC4-R.

55. ~~The method of Claim 1, wherein said composition further comprises an agent that inhibits binding of said POMC compound to an MC4-R.~~

56. ~~The method of Claim 1, wherein said composition further comprises an agent which inhibits said POMC compound from entering the central nervous system of said animal.~~

57. A method for inhibition of free fatty acid uptake and/or stimulation of lipolysis in an animal, comprising administering to the periphery of an animal a POMC compound in an amount effective to produce a result selected from the group consisting of stimulation of lipolysis and inhibition of fatty acid uptake.

58. The method of Claim 57, wherein said amount is insufficient to cause a statistically significant change in the appetite of said animal after administration of said compound as compared to before administration of said compound.

*Survivo*

59. A method of regulating the body weight of an animal, comprising administering to an animal a POMC compound in an amount effective to bind to POMC receptors expressed by said animal in said animal's peripheral tissues, said effective amount:

(a) being insufficient to substantially change the appetite of said animal after said step of administering as compared to before said step of administering;

(b) being between about 0.1  $\mu$ g and about 10 mg per kg of body weight of said animal;

(c) being sufficient to affect a biological activity selected from the group consisting of:

(i) lipolysis; and,

(ii) uptake of fatty acids by adipocytes in said animal; and,

(d) being effective to measurably increase or decrease the body weight of said animal after said compound has been administered to said animal.

60. A method to regulate body weight in an animal, comprising modulating the activity of a melanocortin receptor selected from the group consisting of melanocortin 2-receptor and melanocortin 5-receptor.

61. The method of Claim 60, wherein said melanocortin receptor is melanocortin 2-receptor.

62. The method of Claim 60, wherein said step of modulating comprises administering to the periphery of said animal a compound which regulates said melanocortin receptor.

63. The method of Claim 62, wherein said compound is selected from the group consisting of a POMC compound, an antibody that selectively binds to said melanocortin receptor, and a soluble melanocortin receptor.

64. The method of Claim 60, wherein said step of modulating comprises administering an effective amount of a compound that increases expression of the melanocortin 2-receptor and induces weight loss.

65. The method of Claim 60, wherein said step of modulating comprises administering an effective amount of a compound that decreases expression of the melanocortin 2-receptor and induces weight gain.

66. A method for regulating metabolic efficiency in an animal, comprising:

- (a) measuring serum MSH levels in an animal;
- (b) identifying animals having serum MSH levels of less than about 0.1

ng/ml; and,

(c) administering to the periphery of said animals identified in (b) a composition comprising a compound selected from the group consisting of a POMC compound and leptin, wherein said compound is administered in an amount effective to increase serum MSH levels in said animal to level effective to produce a result selected from the group consisting of stimulating lipolysis and inhibiting fatty acid uptake in said animal.

67. The method of Claim 66, wherein said compound is administered in an amount effective to produce a measurable decrease in body weight of said animal.



68. A therapeutic composition that regulates the peripheral melanocortinergic and/or leptinergic pathways of energy homeostasis in an animal, comprising:

- Sub a12* }
- a. a first body weight regulating agent that is a proopiomelanocortin (POMC) compound; and,
  - b. a second body weight regulating agent that is not a proopiomelanocortin (POMC) compound.

69. The therapeutic composition of Claim 68, wherein said POMC compound is a melanocortin compound.

*Sub a13* } 70. The therapeutic composition of Claim 68, wherein said POMC compound is selected from the group consisting of melanocyte stimulating hormone (MSH), a fragment of MSH, a homologue of MSH, a peptide mimetic of MSH, a non-peptide mimetic of MSH, and a fusion protein comprising an MSH protein or fragment thereof.

71. The therapeutic composition of Claim 68, wherein said POMC compound is selected from the group consisting of  $\alpha$ -MSH,  $\beta$ -MSH and  $\gamma$ -MSH.

72. The therapeutic composition of Claim 68, wherein said POMC compound is a peptide mimetic of MSH.

*Sub a14* } 73. The therapeutic composition of Claim 68, wherein said POMC compound is an analog of a peptide having an amino acid sequence represented herein by SEQ ID NO:2.

74. The therapeutic composition of Claim 68, wherein said POMC compound is an  $\alpha$ -MSH analog selected from the group consisting of:

- a. [Ac-Cys<sup>4</sup>, D-Phe<sup>7</sup>, Cys<sup>10</sup>]  $\alpha$ -MSH, wherein said Cys residues are connected by a disulphide bond;
- b. Ac-[Nle<sup>4</sup>, X<sub>aa</sub><sup>5</sup>, His<sup>6</sup>, X<sub>aa</sub><sup>7</sup>, Arg<sup>7</sup>, Trp<sup>9</sup>, X<sub>aa</sub><sup>10</sup>]-NH<sub>2</sub>, (SEQ ID NO:3)  
wherein X<sub>aa</sub><sup>5</sup> is Glu or Asp, X<sub>aa</sub><sup>7</sup> is Phe or D-Phe and X<sub>aa</sub><sup>10</sup> is a dibasic amino acid; Lys; ornithine; 2,4,-diaminobutyric acid; or 2,3 diaminopropionic acid (Dpr);
- c. Ac-[Cys<sup>4</sup>, Cys<sup>10</sup>]  $\alpha$ -MSH<sub>1-13</sub>NH<sub>2</sub>;
- d. R<sub>1</sub>-W-X-Y-Z-R<sub>2</sub>,

10 wherein R<sub>1</sub> is selected from the group consisting of Ac-Gly-, Ac-Met-Glu-, Ac-Nle-Glu- and Ac-Tyr-Glu-;

W is selected from the group consisting of -His- and -D-His-;

X is selected from the group consisting of -Phe-, -D-Phe-, -Tyr-, -D-Tyr-, (-pNO<sub>2</sub>)D-Phe<sup>7</sup>-;

15 Y is selected from the group consisting of -Arg- and -D-Arg-;

Z is selected from the group consisting of -Trp- and -D-Trp-; and,

R<sub>2</sub> is selected from the group consisting of -NH<sub>2</sub>, -Gly-NH<sub>2</sub>, and -Gly-Lys-NH<sub>2</sub>;

e. Ac-Ser-Tyr-Ser-M-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (SEQ ID NO:4),

20 wherein M is selected from the group consisting of Met, Nle, and Cys;

f. [Nle<sup>4</sup>, D-Phe<sup>7</sup>]-α-MSH;

g. [Nle<sup>4</sup>, D-Phe<sup>7</sup>]-α-MSH<sub>4-10</sub>;

h. [Nle<sup>4</sup>, D-Phe<sup>7</sup>]-α-MSH<sub>4-11</sub>;

25 i. [Nle<sup>4</sup>, D-Phe<sup>7</sup>, D-Trp<sup>9</sup>]-α-MSH<sub>4-11</sub>;

j. [Nle<sup>4</sup>, D-Phe<sup>7</sup>]-α-MSH<sub>4-9</sub>;

k. Ac-[Nle<sup>4</sup>, AA<sup>5</sup>, D-Phe<sup>7</sup>, AA<sup>10</sup>]-R<sub>1</sub> or Ac-[Nle<sup>4</sup>, AA<sup>5</sup>, D-Phe<sup>7</sup>, AA<sup>11</sup>]-R<sub>2</sub>;

wherein AA<sup>5</sup> may be either a L- or D- amino acid having an omega amino or carboxyl group in the side chain, e.g., α,γ-diaminopropionic acid, α,γ-diaminobutyric acid, Orn, Lys, α,β-amino adipic acid, α-aminopimelic acid, or higher  
30 homologs, Glu or Asp;

wherein AA<sup>10</sup> may be diaminopropionic acid, α,γ-diaminobutyric acid, Orn, Lys, α,β-amino adipic acid, α-aminopimelic acid, or higher homologs, Glu or Asp;

35 wherein R<sub>1</sub> is the designation α-MSH<sub>1-13</sub>NH<sub>2</sub>, α-MSH<sub>1-12</sub>NH<sub>2</sub>, α-MSH<sub>1-11</sub>NH<sub>2</sub>, α-MSH<sub>4-13</sub>NH<sub>2</sub>, or α-MSH<sub>4-10</sub>NH<sub>2</sub>;

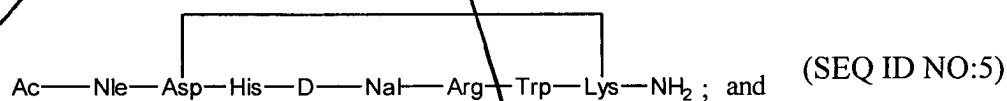
wherein  $AA^{11}$  may be L- or D- amino acid having an omega-amino or carboxyl group in the side chain, e.g.,  $\alpha,\beta$ -diaminopropionic acid;  $\alpha,\gamma$ -diaminobutyric acid, Orn, Lys,  $\alpha$ -amino adipic acid,  $\alpha$ -aminopimelic acid, or higher homologs, Glu or Asp;

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wherein  $R_2$  is the designation  $\alpha$ -MSH<sub>1-13</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>1-12</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>1-11</sub>NH<sub>2</sub>,  $\alpha$ -MSH<sub>4-13</sub>NH<sub>2</sub>, or  $\alpha$ -MSH<sub>4-10</sub>NH<sub>2</sub>; and,

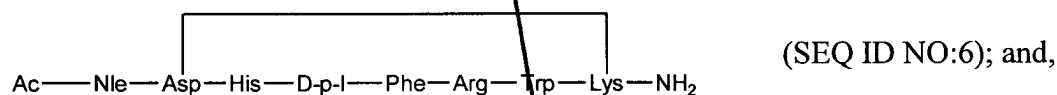
wherein Xxx may be from 1 to 5  $\alpha$ -amino acid residues each of which may be of L- or D- configuration, or a linear or branched chain spacer;

1.

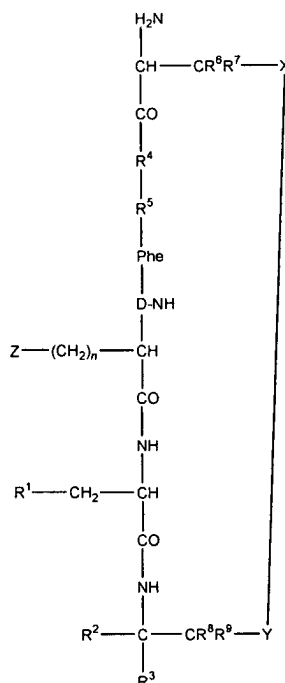


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m.



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wherein  $\text{R}^1$  is a substituted or unsubstituted aromatic radical;

$\text{R}^2$  is hydrogen or a methyl group;

$\text{R}^3$  is a carboxylate, carboxamide, hydroxymethyl, or aldehyde group;

$\text{R}^4$  is glutamic acid, alanine, -amino butyric acid, valine, leucine or isoleucine;

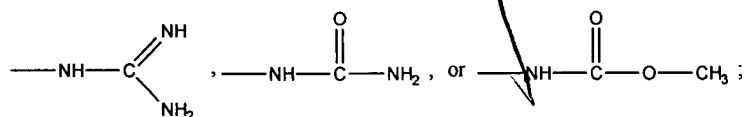
$\text{R}^5$  is histidine, glutamic acid, alanine, valine, leucine or isoleucine;

$\text{R}^6$  and  $\text{R}^7$ , which may be the same or different, are hydrogen, methyl or lower alkyl having one to five carbon atoms;

$\text{R}^8$  and  $\text{R}^9$ , which may be the same or different, are hydrogen, methyl or lower alkyl having one to five carbon atoms;

X and Y are sulfur, methylene, SO or  $\text{SO}_2$ ;

Z is  $-\text{NH}_2$ ,

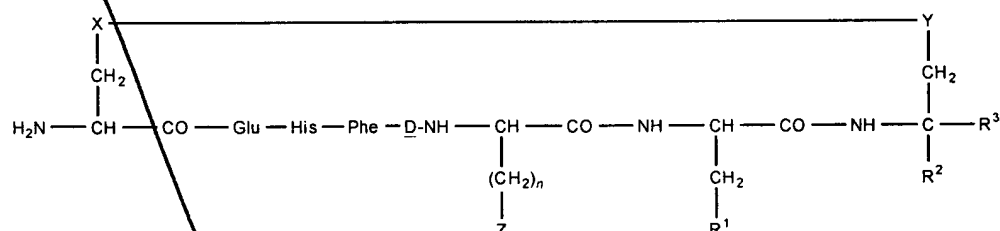


and,

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n is an integer greater than or equal to 2;

O.



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wherein R<sup>1</sup> is phenyl, indole, p-hydroxyphenyl, p-aminophenyl, imidazole, 1-naphthyl  
adamantyl or alkylphenyl, 2-naphthyl;

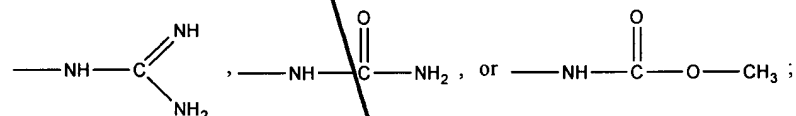
R<sup>2</sup> is hydrogen or a methyl group;

R<sup>3</sup> is a carboxylate, carboxamide, hydroxymethyl, or aldehyde group;

X and Y are sulfur, methylene, SO or SO<sub>2</sub>;

Z is -NH<sub>2</sub>,

75



and,

n is an integer greater than or equal to 2; and wherein the cyclized portion of the  
compound is conformationally restricted in a manner which is compatible with the reactivity  
of the compound with receptors of the central nervous system.

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75. The therapeutic composition of Claim 68, wherein said POMC compound is  
a peptide comprising an amino acid sequence represented by SEQ ID NO:1.

76. The therapeutic composition of Claim 68, wherein said POMC compound  
binds to melanocortin-2 receptors (MC2-R) with a higher affinity than to melanocortin-4  
receptors (MC4-R).

77. The therapeutic composition of Claim 68, wherein said POMC compound binds to MC2-R, and does not bind to any other melanocortin receptor under physiological conditions.

78. The therapeutic composition of Claim 68, wherein said POMC compound does not bind to MC4-R under physiological conditions.

79. The therapeutic composition of Claim 68, wherein said POMC compound does not activate MC4-R under physiological conditions.

*Sub 915* 80. The therapeutic composition of Claim 68, wherein said composition comprises said POMC compound in a dose of from about 0.1 µg to about 10 mg per kg body weight of an animal to which said composition is to be administered.

81. The therapeutic composition of Claim 68, wherein said composition comprises said POMC compound is administered in a dose of from about 1 µg to about 10 mg per kg body weight of an animal to which said composition is to be administered.

82. The therapeutic composition of Claim 68, wherein said composition comprises said POMC compound is administered in a dose of from about 40 µg to about 1 mg per kg body weight of an animal to which said composition is to be administered.

83. The therapeutic composition of Claim 68, wherein said POMC compound is from about 0.1% to about 99% of said therapeutic composition by weight.

84. The therapeutic composition of Claim 68, wherein said POMC compound is from about 0.1% to about 1% of said therapeutic composition by weight.

*Sub 916* 85. The therapeutic composition of Claim 68, wherein said second body weight regulating agent is leptin.

86. The therapeutic composition of Claim 85, wherein said composition comprises a ratio of said POMC compound to leptin of 1:100.

87. The therapeutic composition of Claim 85, wherein said composition comprises a ratio of said POMC compound to leptin of 1:25.

88. The therapeutic composition of Claim 85, wherein said composition comprises a ratio of said POMC compound to leptin of 1:10.

89. The therapeutic composition of Claim 85, wherein said composition comprises said leptin in a dose of from about 0.1  $\mu$ g to about 100 mg per kg body weight of said animal.

90. The therapeutic composition of Claim 85, wherein said composition comprises said leptin in a dose of from about 0.1  $\mu$ g to about 10 mg per kg body weight of said animal.

91. The therapeutic composition of Claim 85, wherein said composition comprises said leptin in a dose of from about 1  $\mu$ g to about 10 mg per kg body weight of said animal.

92. The therapeutic composition of Claim 68, wherein said second body weight regulating agent is selected from the group consisting of an anabolic steroid, a growth hormone, erythropoietin, a cytokine, and an anti-cytokine agent.

93. The therapeutic composition of Claim 68, further comprising a pharmaceutically acceptable excipient.

94. The therapeutic composition of Claim 93, wherein said pharmaceutically acceptable excipient prolongs the presence of said therapeutic composition in the bloodstream of a animal.

*Sub 2.17* 95. A method for treating an affective and mood disorder in an animal, comprising administering to an animal at risk for or suffering from an affective mood disorder a therapeutic composition comprising a proopiomelanocortin (POMC) compound, wherein said POMC compound is administered to the periphery of said animal in an amount effective to measurably ameliorate said disorder in said animal, whereby administration of said compound minimizes delivery of said compound to the central nervous system of said animal.

96. The method of Claim 95, wherein said affective and mood disorder is selected from the group consisting of depression and dysthymia.

97. The method of Claim 96, wherein said depression is atypical depression.



Sub B

98. A method to treat an obesity-associated disorder in an animal, comprising administering to an animal suffering from or at risk for an obesity-associated disorder a therapeutic composition comprising a proopiomelanocortin (POMC) compound, wherein said POMC compound is administered to the periphery of said animal in an amount effective to measurably decrease body weight or weight gain in said animal, whereby administration of said compound minimizes delivery of said compound to the central nervous system of said animal.

99. The method of Claim 98, wherein said obesity-associated disorder is selected from the group consisting of non-insulin dependent diabetes mellitus, cardiovascular disease, cancer, hypertension, osteoarthritis, stroke, respiratory problems, and gall bladder disease.

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100. A method for treating a reproductive disorder in an animal, comprising administering to an animal at risk for or suffering from a reproductive disorder a therapeutic composition comprising a proopiomelanocortin (POMC) compound, wherein said POMC compound is administered to the periphery of said animal in an amount effective to prevent or ameliorate said disorder, whereby administration of said compound minimizes delivery of said compound to the central nervous system of said animal.

101. The method of Claim 100, wherein said reproductive disorder is selected from the group consisting of amenorrhea, an inability or reduced ability to ovulate, an inability to conceive, an inability or reduced ability to maintain a pregnancy, an inability or reduced ability to lactate, an inability or reduced ability to deliver a full-term offspring, and an inability or reduced ability to impregnate a female.

*Sum a20*

102. A method to control undesired body weight which is a side effect resulting from administration of a pharmaceutical compound, comprising administering to an animal at risk of or suffering from undesired body weight which is a side effect resulting from administration of a pharmaceutical compound, a therapeutic composition comprising a proopiomelanocortin (POMC) compound wherein said POMC compound is administered to the periphery of said animal in an amount effective to measurably decrease body weight or weight gain in said animal, whereby administration of said compound minimizes delivery of said compound to the central nervous system of said animal.

103. The method of Claim 102, wherein said pharmaceutical compound is selected from the group consisting of valproic acid, lithium, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRI).

*add a21**Add c7*

104. A food composition that regulates the peripheral melanocortinergic and/or leptinergic pathways of energy homeostasis, comprising a proopiomelanocortin (POMC) compound.

105. A method to regulate body weight in an animal, comprising feeding to said animal the food composition of Claim 104, wherein said food composition is effective to measurably regulate body weight in said animal, and wherein delivery of said compound to the central nervous system of said animal is minimized.

106. A method to increase the body weight and/or mass in an animal having an eating disorder, comprising administering to said animal a therapeutic composition comprising a proopiomelanocortin (POMC) antagonist compound, wherein said POMC compound is administered to the periphery of said animal in an amount effective to measurably increase body weight or reduce body weight loss in said animal, whereby administration of said compound minimizes delivery of said compound to the central nervous system of said animal.

107. The method of Claim 106, wherein said eating disorder is selected from the group consisting of anorexia and bulimia.

add  
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